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Improved Catalyst Design for the Palladium-Catalyzed Enantioselective Oxidation of Chiral Secondary Alcohols: Access to Both Enantiomeric Series**

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alcohols; asymmetric catalysis; kinetic resolution; oxidation; palladium

Enantioenriched alcohols are ubiquitous in the structures and syntheses of natural products and pharmaceuticals. Catalytic, asymmetric alcohol oxidation can be a useful method to access these molecules.[1] Previously, we reported the development of an aerobic kinetic resolution of alcohols by catalytic [Pd(nbd)Cl_2] (**1**, nbd = norbornadiene) and the naturally occurring alkaloid (−)-sparteine (sp, (−)-**2**) in the presence of molecular oxygen.[2-6] Although this system successfully resolves a wide range of secondary alcohols to high enantiomeric excess, the rates of oxidation for certain substrates are prohibitively slow. Furthermore, the use of **2** as a ligand, which is only commercially available as the (−)-antipode, restricts access to alcohols in one enantiomeric series. [7] Herein, we disclose the development of a catalyst based on an understanding of reaction mechanism that effects dramatic rate increases, thereby

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permitting resolution of a broader range of substrates. This more active catalyst allows the use of an alternative chiral diamine ligand in the resolution, making either enantiomer of secondary alcohols easily obtainable. The utility of the system is demonstrated in the formal total synthesis of *nat*-(−)-amurensinine ((−)-**3**).

Our initial screens of Pd sources revealed dichloride complexes to be superior to acetate and trifluoroacetate.[2] X-ray analyses of a series of crystalline palladium(II) complexes[8] and computational studies of mechanistic pathways[9] led to a better understanding of the role of the halide counterion in the resolution. The sterically crowded, C_1 symmetric (−)-sparteine ligand induces significant square plane distortion in many palladium complexes (Figure 1).[8] Specifically, for the solid-state structure of [Pd(sp)Cl_2] (**4**), the sum of the six angles around the metal center is 705.99°,[8] compared to 720° for an ideal square planar geometry.[10] The majority of this distortion is due to deflection of X^2 away from the projecting piperidine ring of (−)-**2**. For dichloride complex **4**, X^2 is 9.9° out of the plane. This deformation is even more pronounced in the structure of a palladium alkoxide that mimics a proposed alcohol oxidation intermediate (**7**, R^1 = Ph, R^2 = CF_3, X^2 = Cl, sum of six palladium-ligand angles: 701.58°, X^2 deflection: 15.4°).[8] [Pd(sp)$(OAc)_2$] (**5**), a less active catalyst for the kinetic resolution,[11] has a smaller deviation from ideal square planar geometry (sum of six palladium-ligand angles: 711.40°, X^2 deflection: 5.3°).[12] This (−)-sparteine-induced distortion of X^2 results in a geometry that is more like the transition state (**8**),[9] potentially lowering the energy barrier to β-hydride elimination. Thus, we predicted that palladium complexes with coordinated counterions that display a greater X^2 deflection would serve as more active oxidation catalysts.

This hypothesis inspired us to investigate bromide as a larger, but still coordinating, counteranion. X-ray analysis of a single crystal of [Pd(sp)Br_2] (**6**)[13] revealed a greater deviation of one of the bromides from the Pd square plane (sum of six palladium-ligand angles: 699.22°, X^2 deflection: 14.0°) compared to complex **4**, suggesting the potential for superior reactivity.

Previously, $PdBr_2$ had been examined as a palladium source in this transformation, but rapid formation of a black mixture and low conversion indicated catalyst decomposition at 80 °C. Use of preformed complex **6** is only slightly more successful (Table 1, entry 1). However, in reactions performed at 60 °C or below, dibromide complex **6** is quite stable and catalyzes facile oxidation of secondary alcohols (entry 2) relative to dichloride complex **4** (entry 3).[14] Importantly, high selectivity is maintained in reactions with dibromide **6**.[15] Analogous to our experiments with dichloride complex **4** (entry 4),[3] chloroform proved to be an excellent solvent, affording product ketone at good rates at 23 °C (entry 5).[16]

Oxidative kinetic resolution of a number of secondary alcohols was facile with this $PdBr_2$ system (Table 2). Alcohols previously resolved with dichloride **4**[3] are oxidized much more rapidly with dibromide **6** (entries 1, 3, and 5), and selectivity factors increase at lower temperatures (entries 4 and 5). To our delight, a variety of secondary alcohols that displayed very poor reactivity with **4** are readily oxidized using catalyst **6**. Sterically hindered benzylic alcohols (entries 6–10), allylic alcohols (entry 11), and even less activated saturated alcohols (entries 12 and 13) are resolved to high enantiomeric excess. Furthermore, the use of ambient air instead of pure oxygen as the stoichiometric oxidant is sufficient for a successful resolution (entries 2, 7, 9, and 13).

Encouraged by our success in promoting rapid oxidation with a palladium bromide complex, we began to explore other diamines in the kinetic resolution. Although the availability of (−)-sparteine ((−)-**2**) made it an attractive chiral ligand for the process, the scarcity of its enantriomer (i.e., (+)-**2**) was a major limitation to the broad utility of the method.[17] The insights gained from the investigation of complexes of (−)-**2**, specifically A) the importance

of an electron rich, rigid ligand, B) and the need for an aerobically stable chiral ligand able to induce halide counterion distortion in its corresponding palladium complex, led us to diamine **11**.[18] Prepared in a 3-step sequence from the easily accessible alkaloid (−)-cytisine, **11** was shown to act as a (+)-sparteine mimic in a variety of processes.[19,20]

As in the case of palladium complexes with (−)-**2**, X-ray crystallographic analyses of [Pd(diamine)X_2] reveal a greater counterion distortion for Br compared to Cl with diamine **11** (Figure 2, sums of six palladium-ligand angles and X^1 deflection for **12**: 704.67° and 11.9°, respectively, and for **13**: 701.69° and 14.2°).[13] Indeed, reactions performed with the two catalysts led to disparate results favoring the dibromide **13** (Scheme 1).

Gratifyingly, complex **13** could be generated in situ and resulted in greatly improved reactivity (Table 3). Thus, a variety of benzylic (entries 1–5), allylic (entries 6–10), and cyclopropylcarbinyl (entries 11 and 12) alcohols can be resolved with high selectivity. Ambient air is also a suitable oxidant (entries 2 and 4). Importantly, this protocol yields alcohols in the opposite enantiomeric series to that obtained with (−)-sparteine (**2**).

To further test these results, we investigated a synthetically interesting substrate that had proven challenging for our $PdCl_2$ system. Recently, we reported an enantioselective total synthesis of (+)-amurensinine ((+)-**3**) that employs an oxidative kinetic resolution as a key step to produce an enantioenriched intermediate (i.e., (−)-**14**) en route to the antipode of the natural product.[21] In order to access the naturally occurring enantiomer (i.e., (−)-**3**), we applied diamine **11** to the resolution of (±)-**14**. In the event, use of a dibromide complex provided enantioenriched alcohol (+)-**14** in high yield and excellent enantiomeric excess (s = 27, Scheme 2). This application constitutes a formal total synthesis of natural (−)-amurensinine (**3**).

In conclusion, we have developed a greatly improved oxidative kinetic resolution of secondary alcohols based on an understanding of the factors that contribute to reactivity and selectivity in this process. Furthermore, these improvements have allowed us to employ the alternative diamine ligand **11** in the oxidation to afford alcohols in the enantiomeric series opposite to that obtained with (−)-sparteine. Importantly, solid state X-ray analysis was used extensively as a guide in these studies, providing invaluable insights. Finally, this methodology has been applied to a kinetic resolution of alcohol (±)-**14**, allowing access to the natural enantiomer of the isopavine alkaloid amurensinine. Efforts to further enhance reactivity and selectivity in these oxidations, to use this method in complex molecule synthesis, and to apply these findings to other palladium-catalyzed oxidations are ongoing.

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10. See Supporting Information for details.
11. Oxidations of (+)-**9** conducted with [Pd(sp)X_2] as catalyst displayed the following trend in reactivity: Br > Cl > O_2CCF_3 > I > OAc, see Supporting Information for details.
12. Mueller JA, Sigman MS. J Am Chem Soc 2003;125:7005–7013. [PubMed: 12783555]
13. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies may be obtained on request, free of charge, by quoting the publication citation and the deposition number 298214 for **6**, 274539 for **12**, and 639648 for **13**.
14. Poor reactivity and selectivity were observed in the oxidative kinetic resolution with [Pd(sp)I_2] as catalyst, see Supporting Information for details.
15. The selectivity factor s was determined using the equation $s = k_{fast}/k_{slow} = \ln[(1-C)(1-ee)]/\ln[(1-C)(1+ee)]$, where C is conversion, see: ref [6a].
16. The reactivity of **6** in chloroform was comparable to complexes prepared in situ from a variety of $PdBr_2$ sources, see Supporting Information for details.
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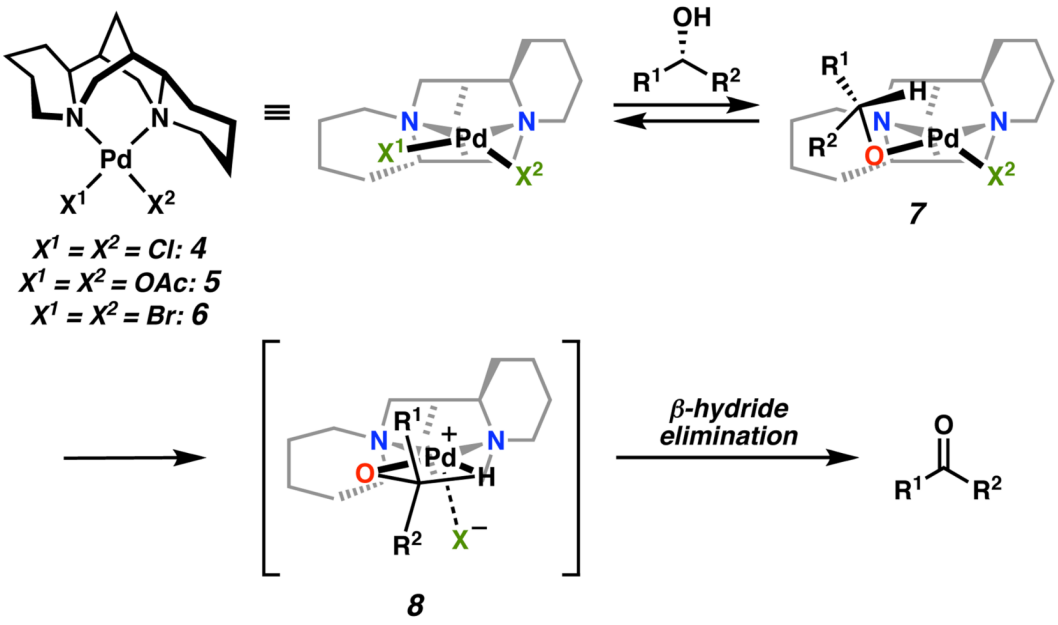


Figure 1.
Alcohol oxidation model with [Pd(sp)X_2].

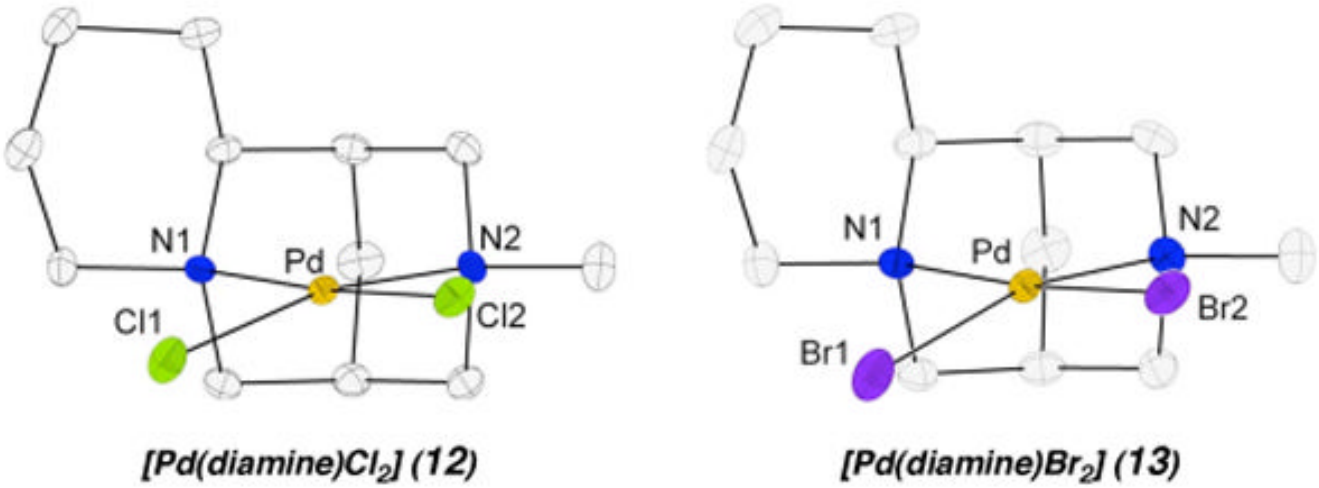
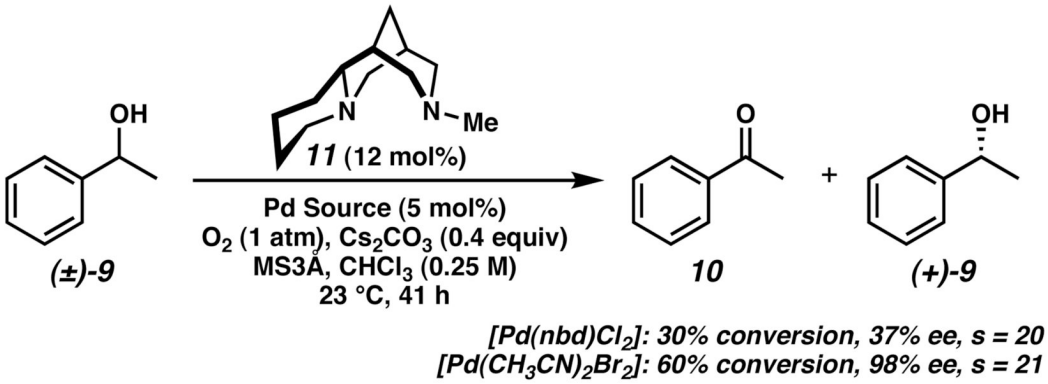
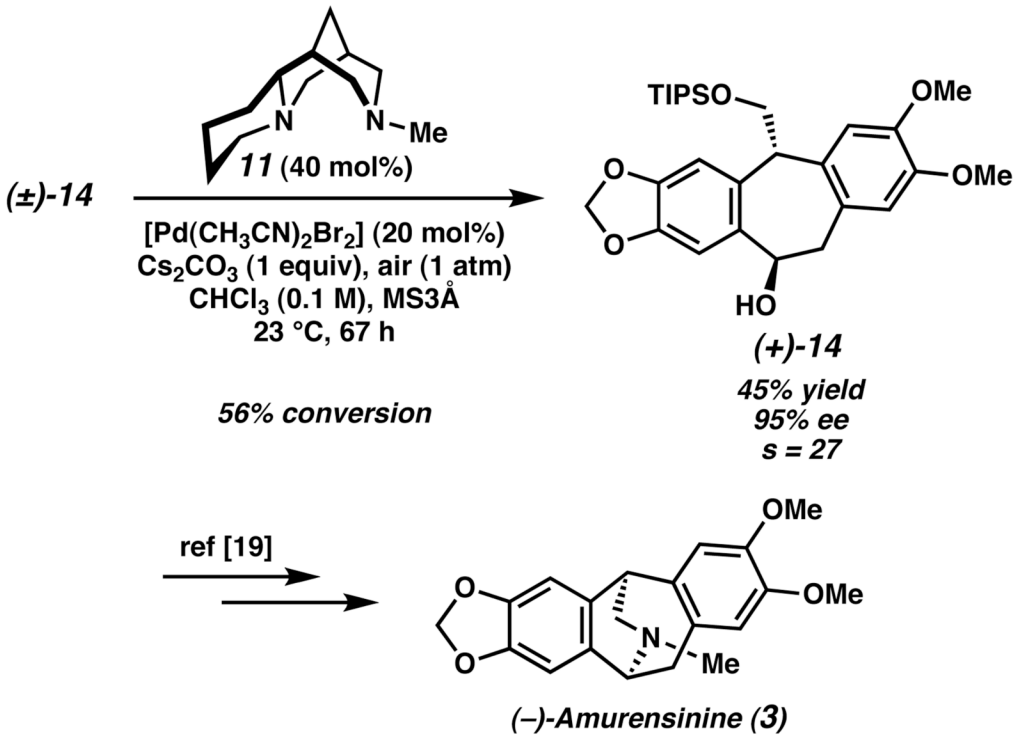


Figure 2.
X-ray structures of [Pd(diamine)X_2].



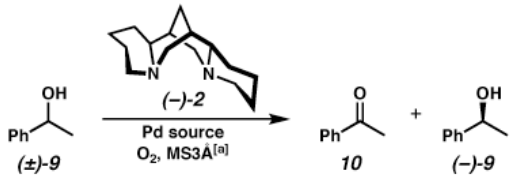
Scheme 1.
Kinetic resolution of (±)-**9** with PdX2 and diamine **11**.



Scheme 2.
Preparation of (+)-**14**.

Table 1

Optimization of conditions with [Pd(sp)X_2].



Entry	Solvent	*T* [°C]	Pd source	*t* [h]	Conversion [%][b]	Alcohol *ee* [%][c]	*s*
1[d,e]	$PhCH_3$	80	[Pd(sp)Br_2] (*6*)	76	32	27	5
2	$PhCH_3$	60	[Pd(sp)Br_2] (*6*)	9	58	99	29
3	$PhCH_3$	60	[Pd(sp)Cl_2] (*4*)	24	54	90	21
4[f]	$CHCl_3$	23	[Pd(sp)Cl_2] (*4*)	48	60	99	31
5[f]	$CHCl_3$	23	[Pd(sp)Br_2] (*6*)	4	56	96	28

[a] 5 mol% Pd source, 15 mol% (−)-sparteine, 1 atm O_2, 0.25 M in solvent, unless otherwise noted.

[b] Determined by GC.

[c] Determined by chiral HPLC.[10]

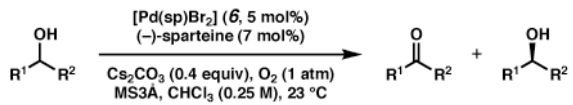
[d] 0.1 M in $PhCH_3$.

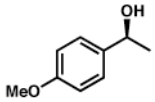
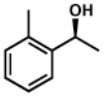
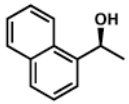
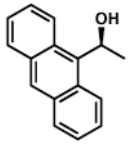
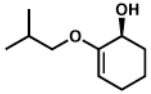
[e] Pd black observed.

[f] 7 mol% (−)-sparteine, 40 mol% Cs_2CO_3. MS3Å = 3Å molecular sieves.

Table 2

Resolution of a variety of alcohols with [Pd(sp)Br_2] (**6**).



Entry	Alcohol (Major Enantiomer)	*t* [h] Conversion [%][a] (Yield [%])[b]	Alcohol ee [%][c]	*s*
1		456 (43)	96	28
2[d]		555	95	27
3		459 (41)	95	17
4[e]		859	97	20
5[f]		2460	98	20
6		4164 (35)	97	14
7[d]		3063	96	13
8		2460 (40)	93	14
9[d]		2165	99	15
10		1560	91	12
11		4862	97	16
12		4958 (40)	91	15
13[d]		4558	91	15

[a] Determined by GC or ^{1}H NMR.

[b] Isolated yield of enantioenriched alcohol.

[c] Determined by chiral HPLC or GC.[10]

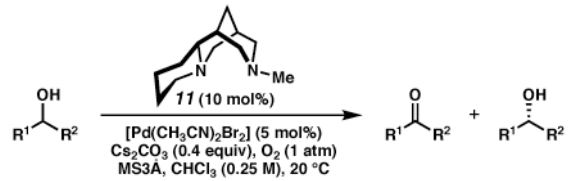
[d] Performed under ambient air.

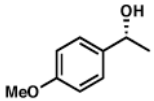
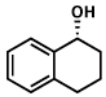
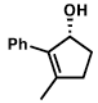
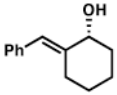
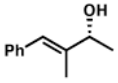
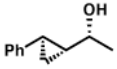
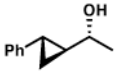
[e] Performed at 10 °C.

[f] Performed at 4 °C.

Table 3

Resolution of alcohols with $[Pd(CH_3CN)_2Br_2]$ and diamine **11**.



Entry	Alcohol (Major Enantiomer)	*t* [h]	Conversion [%][a] (Yield [%])[b]	Alcohol *ee* [%][c]	*s*
1		30	58 (40)	97	25
2[d]		34	58	96	22
3		30	60	98	19
4[d]		34	61	98	19
5		24	61 (38)	90	11
6		46	57 (43)	91	17
7		12	55	94	27
8		18	63	94	12
9		46	59 (39)	91	13
10		35	63	92	11
11		32	59 (40)	90	13
12		35	62	90	10

[a] Determined by GC or ^{1}H NMR.

[b] Isolated yield of enantioenriched alcohol.

[c] Determined by chiral HPLC or GC.[10]

[d] Performed under ambient air.